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AN ATTEMPT TO SYNTHESIZE SOME THYROXINE
-LIKE COMPOUNDS

by

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Department of Chemistry

University of Alberta

A THESIS

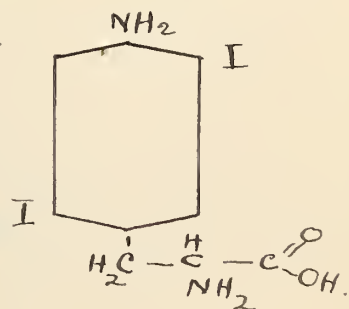
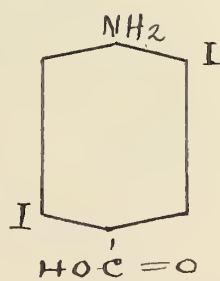
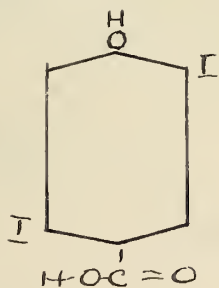
Submitted to the Committee on
Graduate Studies, University of
Alberta, in partial fulfilment
of the requirements for the
degree of Master of Science.

AN ATTEMPT TO SYNTHESIZE SOME THYROXINE -LIKE COMPOUNDS

This investigation was intended to be a continuation of that undertaken by Wray V. Drake¹, 1929-1930.

When a naturally occurring compound which has a definite physiological action has been prepared synthetically the organic chemist tries, to simplify the structure, to make the compound more potent and to arrive at some agreement between structure and physiological action. Because of the successful synthesis of thyroxine by Harrington and Barger² in 1926, it was decided to attempt to follow up the above ideas in connection with thyroxine.

From the structure of thyroxine it is interesting to note that the molecule contains positive iodine. Might not the activity of this compound be due to the peculiar combination of positive and negative iodines in the same molecule? In order to study this and in some measure to simplify the structure the following compounds are being prepared in this laboratory:-



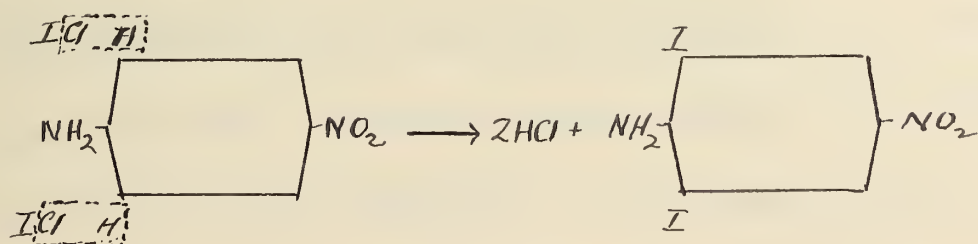
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1. R. B. Sandin and W. V. Drake, J.A.C.S., 52, 3353 (1930).
 2. C. S. Harrington and G. Barger, Biochem. J., 21, 169 (1927).

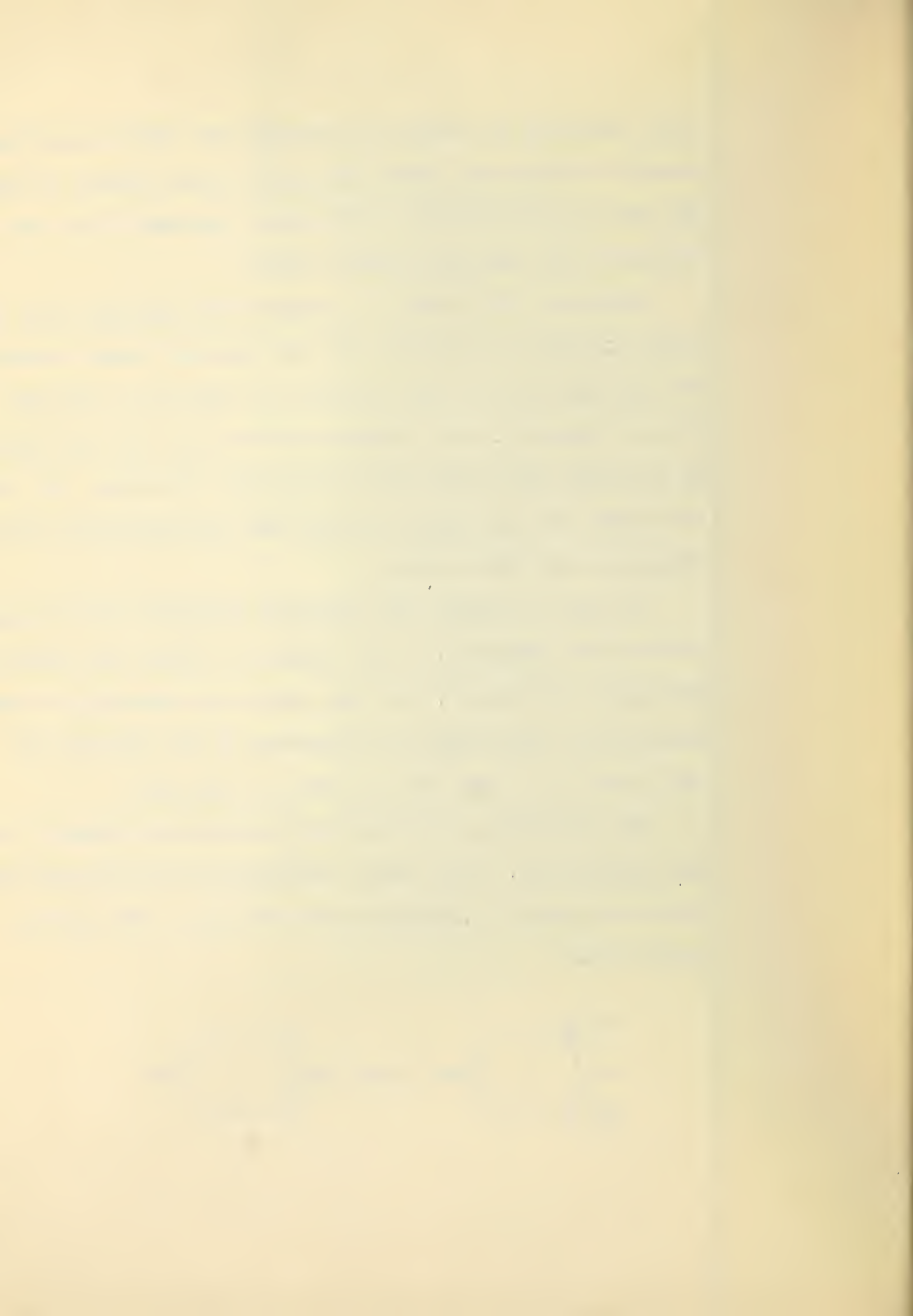
These molecules are simple in structure and contain positive and negative iodines and include the basic groups present in thyroxine. The work on the synthesis of the above compounds is not far enough advanced to be included in this report.

Similarly the attempts to prepare thio-thyroxine viz; the sulfur analogue of thyroxine and the thyroxine isomer containing the hydroxyl-group in meta position as compared to the para position in thyroxine, were attempted in the hope that one compound or the other might prove more potent than thyroxine. The attempt to prepare thio-thyroxine has been done in co-operation with T. B. Johnson at Yale University.

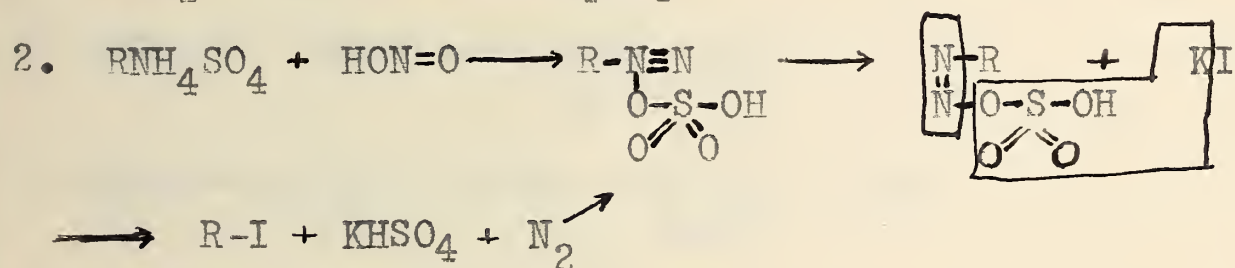
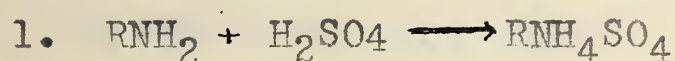
In order to acquire the technique necessary for the synthesis of the above compounds, it was decided to follow the procedure of Harrington and Barger², and study each step thoroughly to master any difficulties which might be encountered in the synthesis of thyroxine itself or of the other postulated compounds.

The procedure, as outlined by Harrington and Barger, presented few difficulties. From iodine monochloride and p-nitroaniline, there was prepared 2,6-diiodo-p-nitroaniline. The reaction is as shown below:-

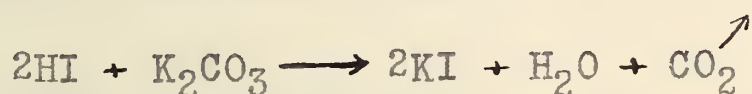
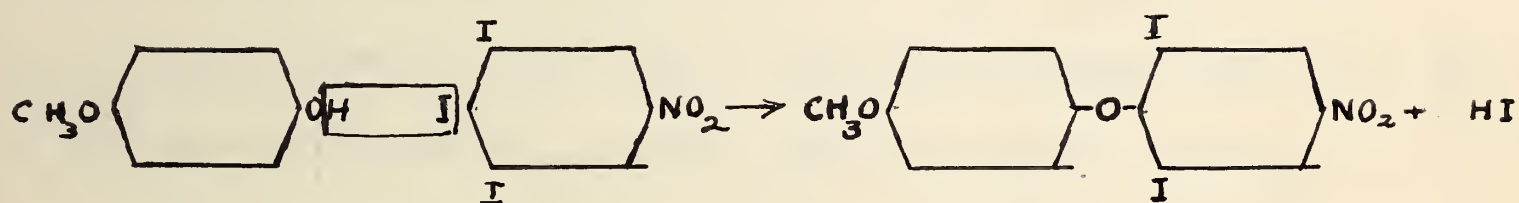




By the diazotization of the above compound by sodium nitrite and the addition of potassium iodide 3,4,5-triiodonitrobenzene was prepared. The reaction is shown below where R- represents the 2,6-diiodo-4-nitro- radical:-

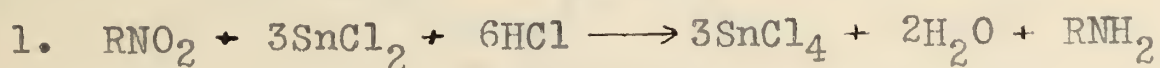


The reaction between 3,4,5-triiodonitrobenzene and hydroquinone monomethyl ether, in boiling methyl ethyl ketone, in the presence of potassium carbonate, proceeds as below:-

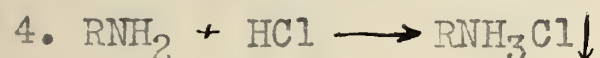


It was necessary in this case to use an excess of hydroquinone monomethyl ether and potassium carbonate to secure a good yield of the desired compound. These were removed from the product by steam distillation and solution.

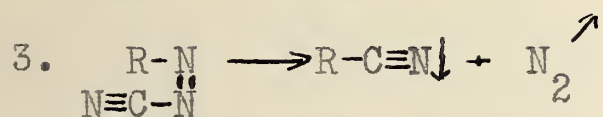
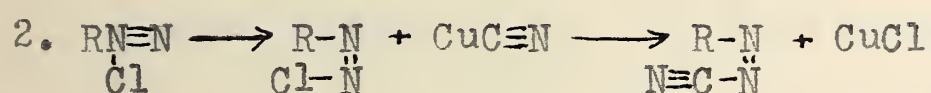
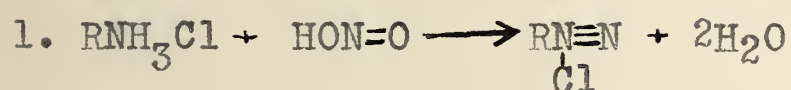
The reduction of the nitro compound by stannous chloride and hydrogen chloride is shown below, where the radical 3,5-diiodo-4-(4'-methoxyphenoxy)-phenyl- is represented by R- :-



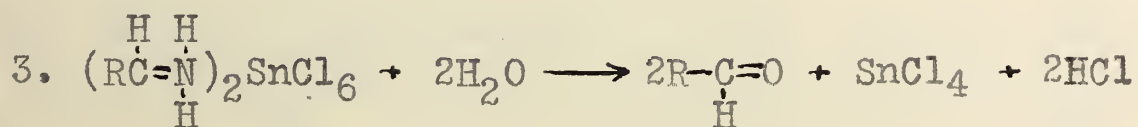
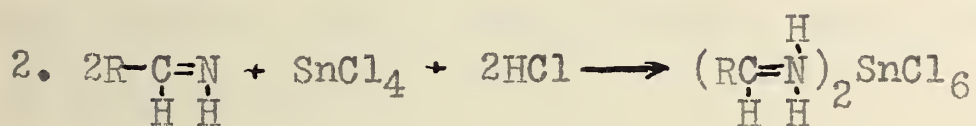
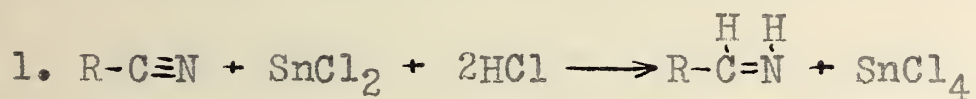
This amine may be precipitated from an ethereal solution by the use of dry hydrogen chloride:-



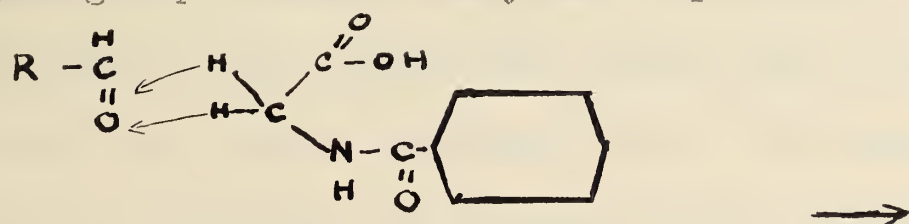
The next stage was very difficult. It is a modification of the Sandmeyer reaction:-

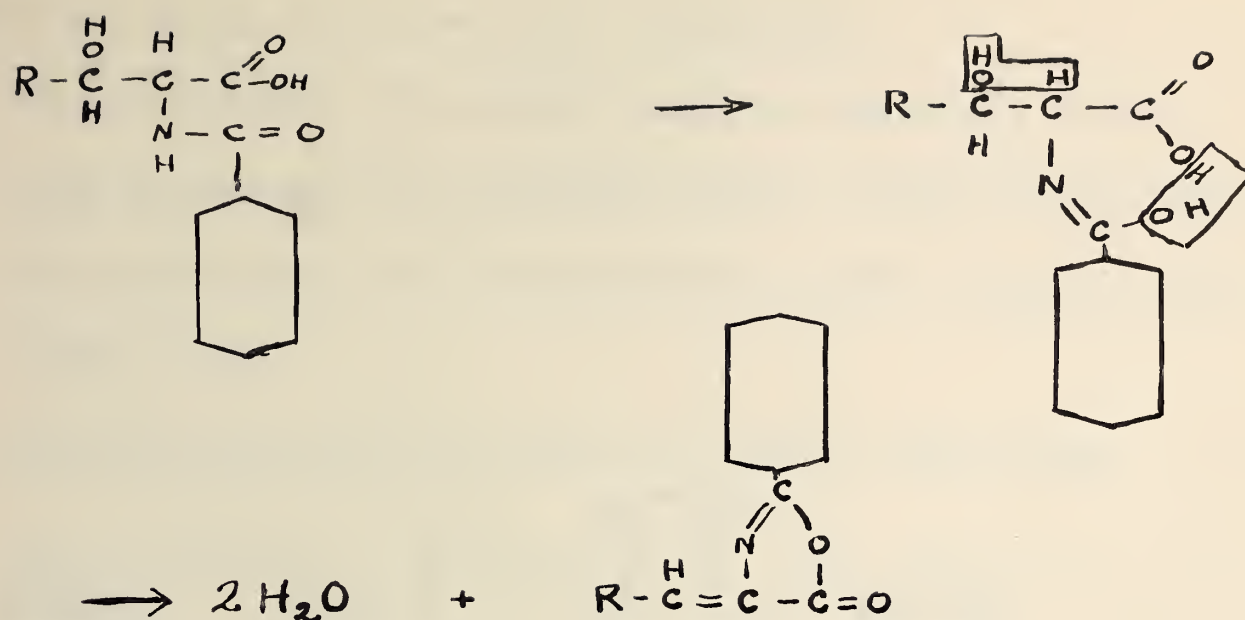


The above nitrile may pass through the Stephen's reaction, which involves a breaking of the triple bond between the carbon and nitrogen atoms, by the use of anhydrous stannous chloride and dry hydrogen chloride in an ether and chloroform solution.



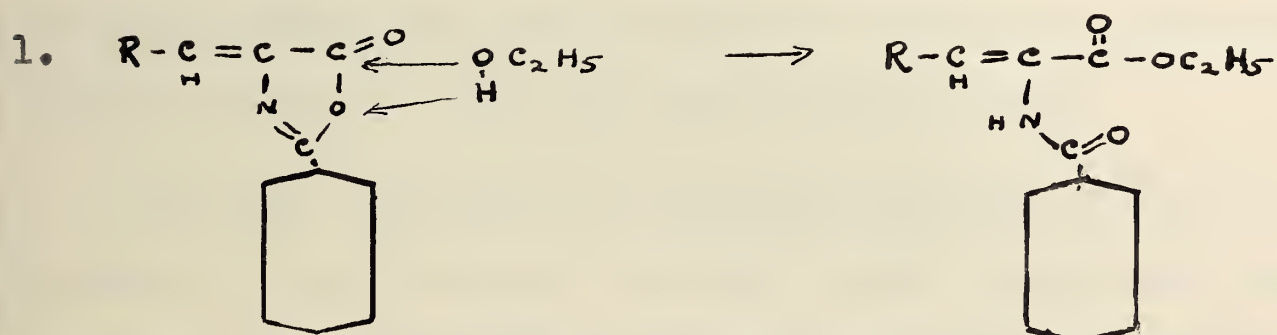
All aromatic aldehydes will pass through the Erlenmeyer Jr. reaction, which involves the addition of an α -amino acid to the aldehyde group in such a way as to produce an azlactone:-





This reaction is carried out in the presence of sodium acetate, as a probable catalyst, and acetic anhydride as a solvent and as a probable dehydrating agent. In carrying out this reaction, it is necessary that the temperature of the reaction be kept below 100° or the aldehyde and sodium acetate combine to give a cinnamic acid.

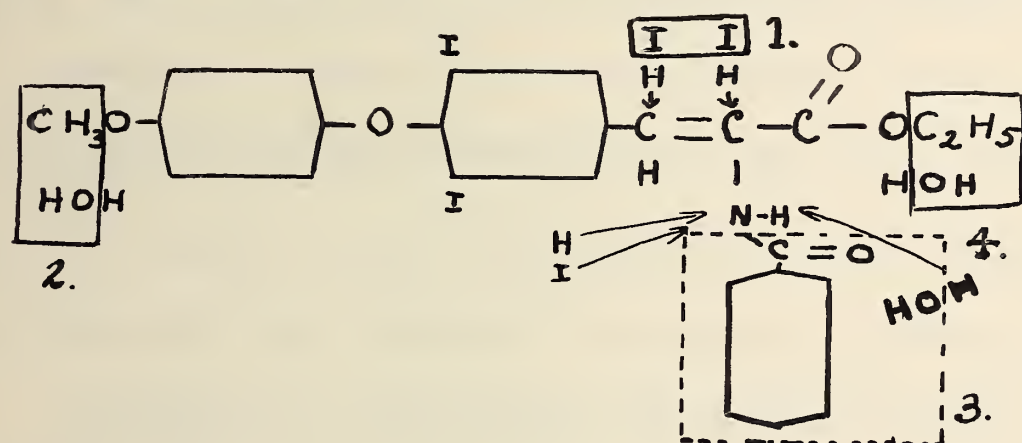
On treating the above azlactone with absolute alcohol containing 10% sulfuric acid, esterification takes place. The probable mechanism is shown below:-



In addition to esterification, this reaction involves a breaking of the double bond between the carbon and nitrogen atoms in the azlactone ring with a reformation of the benzoylamino-group. This is due to a migration of hydrogen from oxygen to nitrogen in the compound.

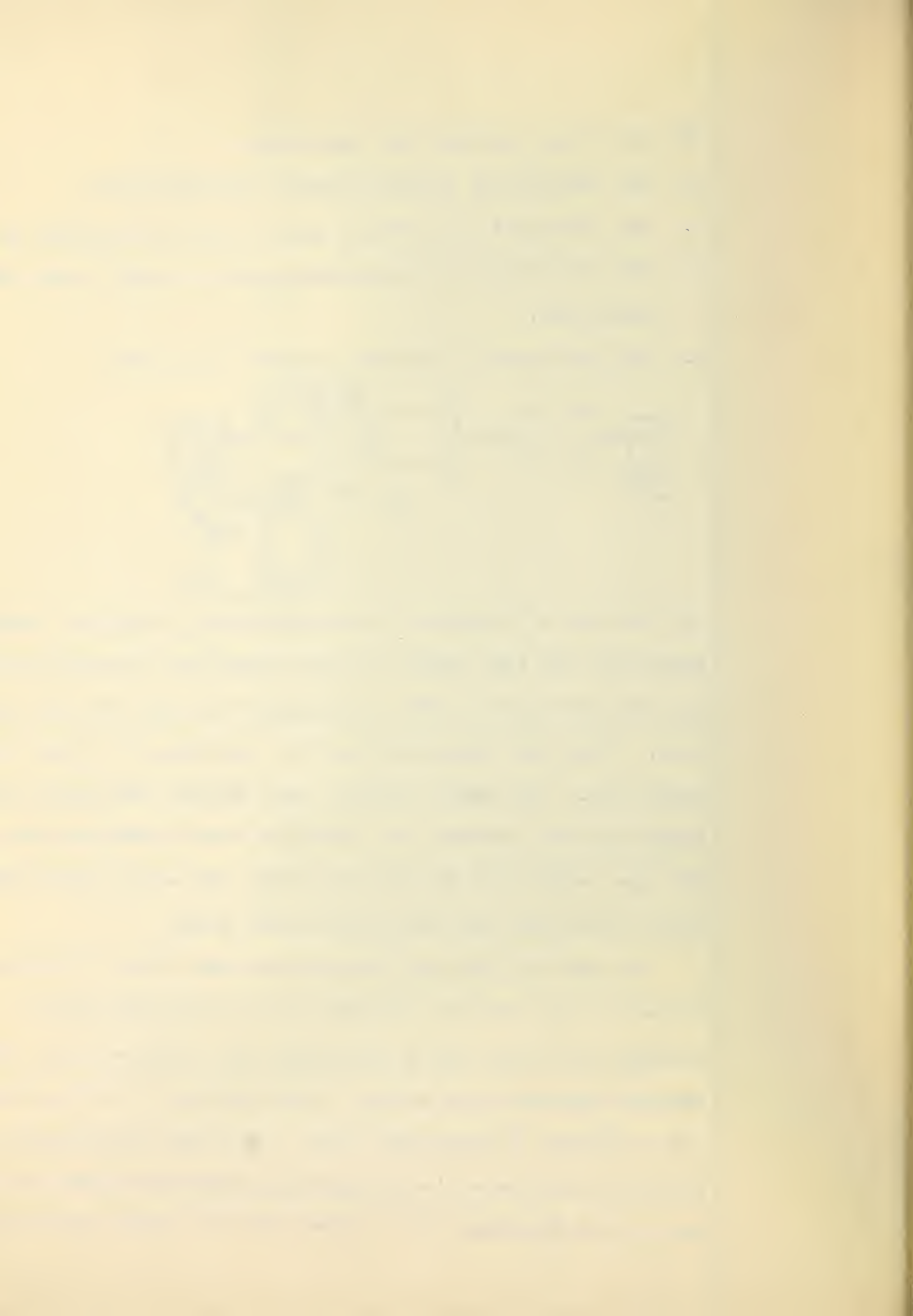
The next stage involves four reactions:-

1. The reduction of a double bond by hydriodic acid,
2. The hydrolysis of a methoxy group to give an hydroxyl group,
3. The hydrolysis of a benzoylamino group to give a salt of an amino acid,
4. The hydrolysis of an ester to give a free acid.

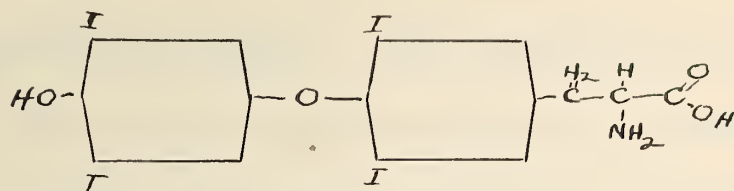


In the case of reaction 1, red phosphorous is used as a catalyst combining with free iodine to give phosphorous triiodide which is in turn hydrolysed to give orthophosphorous acid and more hydriodic acid. Since this step involves four reactions, the yield is necessarily low. The methyl alcohol, ethyl alcohol and benzoic acid formed in this reaction, are distilled from the diiodo-amino acid. The free amino acid may be prepared by the use of sodium acetate, which neutralizes the amino hydroiodide group.

In order to form the tetraiodopropionic acid, it is found convenient to use nitrogen triiodide as the iodinating agent. This reaction is carried out by dissolving the diiodopropionic acid in ammonium hydroxide and adding a slight excess of iodine, dissolved in a solution of potassium iodide. The final compound, β -3',5'-diiodo-3,5-diiodo-4-(4'-hydroxyphenoxy)- α -aminopropionic acid, has been called thyroxine and is formed from the active constituent of



the thyroid gland. It is shown below:-



Since the above amino acid contains an assymetric carbon atom, it is possible to have both dextro-rotatory and laevo-rotatory forms. It appears from the synthesis in the form of the racemate which may be resolved into its optically active forms by combination with an alkaloid, eg; brucine, as used by Harrington and S. S. Randall^{3,4}.

Attempts to synthesize the oxygen isomer, β -4',6'-diiodo-3,5-diiodo-4-(4'-hydroxyphenoxy)- α -aminopropionic acid, and the sulfur isomer, β -3',5'-diiodo-3,5-diiodo-4-(4'-hydroxythiophenoxy)- α -aminopropionic acid, failed at the stage of the preparation of the nitriles from the hydrochlorides of 3,5-diiodo-4-(4'-methoxyphenoxy)-aniline and of 3,5-diiodo-4-(4'-methoxythiophenoxy)-aniline. A number of runs were made in the attempt to form the nitriles. In no one case, was it possible to isolate the corresponding nitriles. Variations of the Sandmeyer reaction, proposed by Korczinski⁵ and McRae⁶, were tried without success. The method used by Korczinski

3. C. R. Harrington and S. S. Randall, Biochem. J., 25, 1028(1931).

4. C. R. Harrington and McArtney, Biochem. J., 21, 853(1927).

5. Korczinski and Fandrich, Comptes Rendues, Avril(1926).

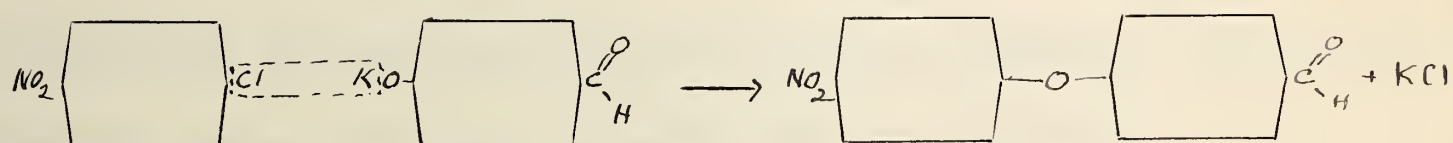
6. McRae, J. A. C. S., 52, 4550(1930).

was one in which nickel cyanide was used in the place of cuprous cyanide as the cyanating agent. The modification proposed by McRae was one in which the excess cuprous cyanide, used in the Sandmeyer reaction, was dissolved in sodium carbonate or sodium hydroxide.

SOME RESEARCH ON THE ERLENMEYER JR. SYNTHESIS OF AMINO ACIDS

It was decided to attempt to prepare some β -substituted- α -aminopropionic acids and to study the Erlenmeyer Jr. synthesis as related to these aldehydes.

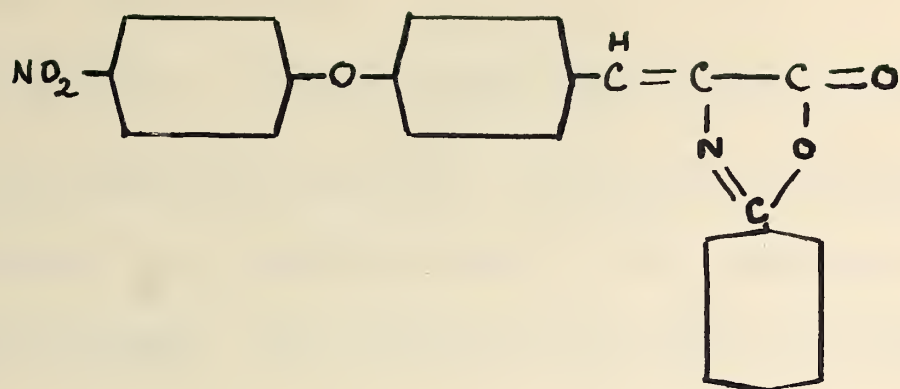
Various derivatives of 4-(4'-nitrophenoxy)-benzaldehyde prepared by Suter⁷ were made. The above compound was prepared by a Williamson's synthesis of an ether. P-nitrochlorobenzene reacted with the potassium salt of p-hydroxybenzaldehyde as shown below:-



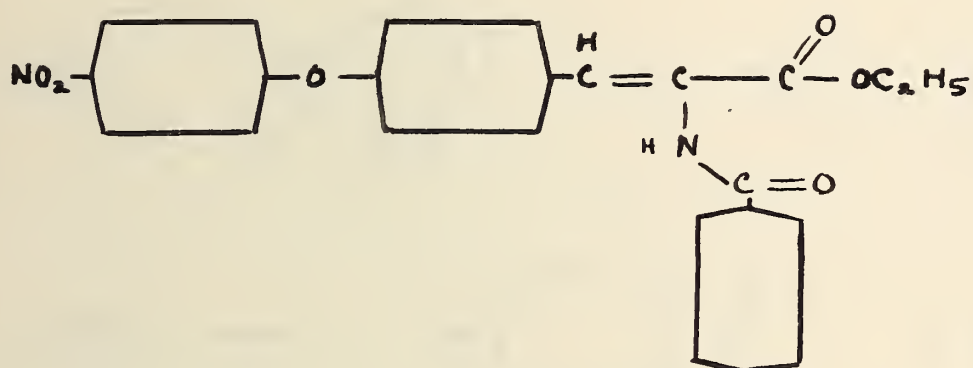
It was found necessary to carry out the reaction in the presence of excess p-nitrochlorobenzene, which was later removed by steam distillation. The product was purified by recrystallization from dilute acetic acid or alcohol.

The above aldehyde went through the Erlenmeyer Jr. reaction, involving the combination of the aldehyde with hippuric acid to produce an azlactone of the following composition:-

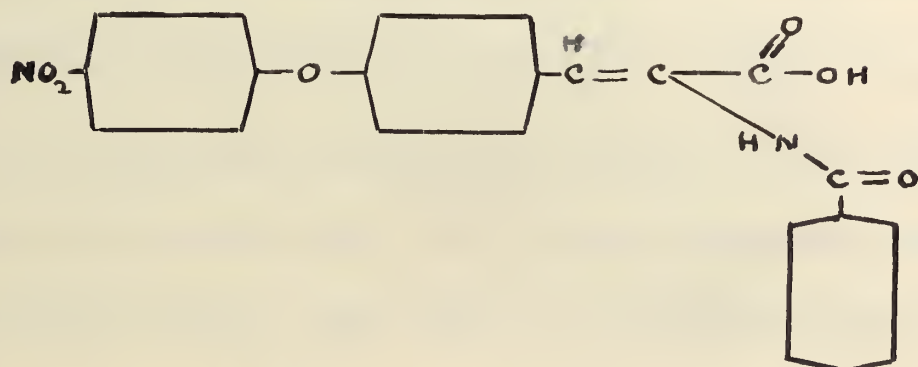
7. Suter and Oberg, J. A. C. S., 53, 1566(1931).



The above azlactone was esterified by the use of ethyl alcohol with sulfuric acid as a catalyst. The compound 4-(4'-nitrophenoxy)- α -benzoylamino-cinnamic acid ethylester as shown below, was formed:-



By refluxing the above ester or the above azlactone with dilute sodium hydroxide and neutralizing with dilute sulfuric acid 4-(4'-nitrophenoxy)- α -benzoylamino cinnamic acid was formed:-

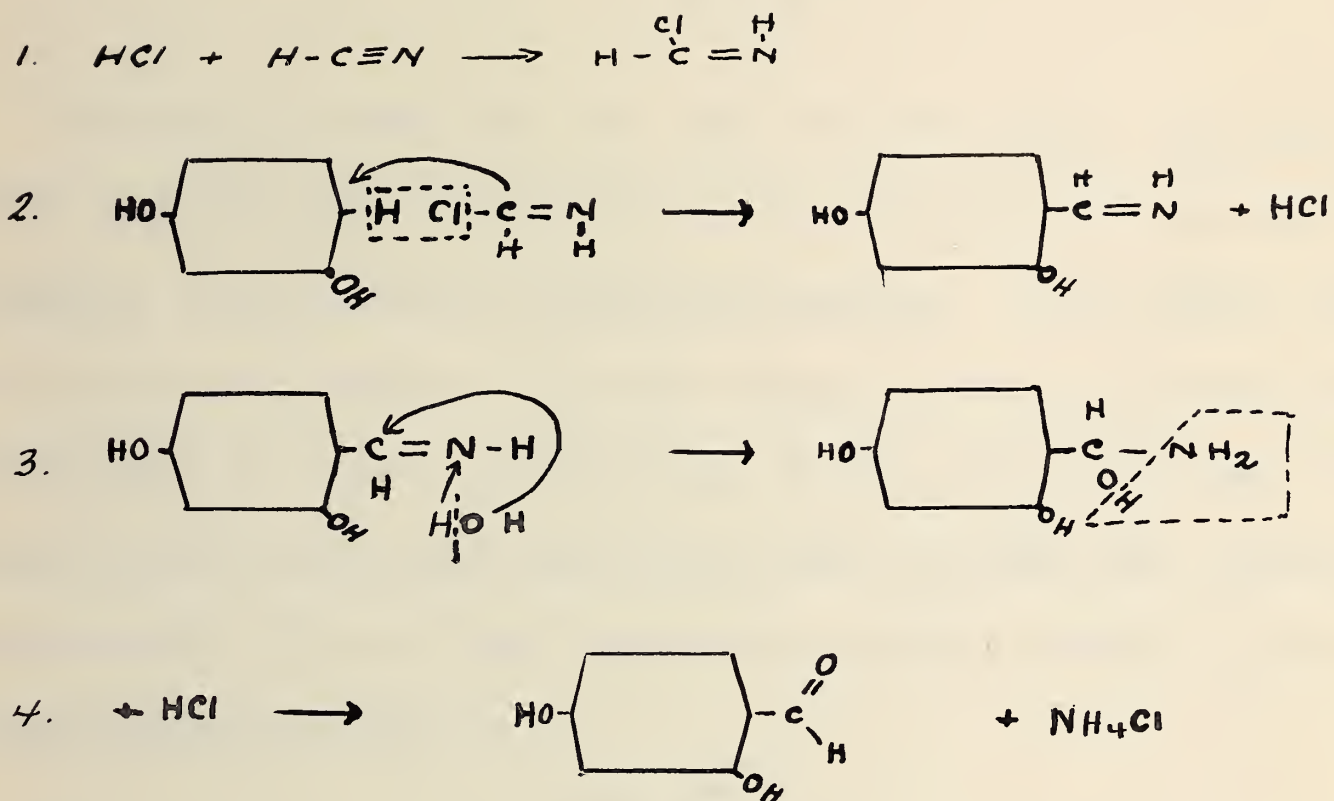


Harrington^{3,4} prepared 3,4-dihydroxyphenylalanine and Lamb and Robson⁸ made a number of modifications in the Erlenmeyer Jr. syn-

8. Lamb and Robson, Biochem. J. 25, 1231(1931)

thesis of amino acids.

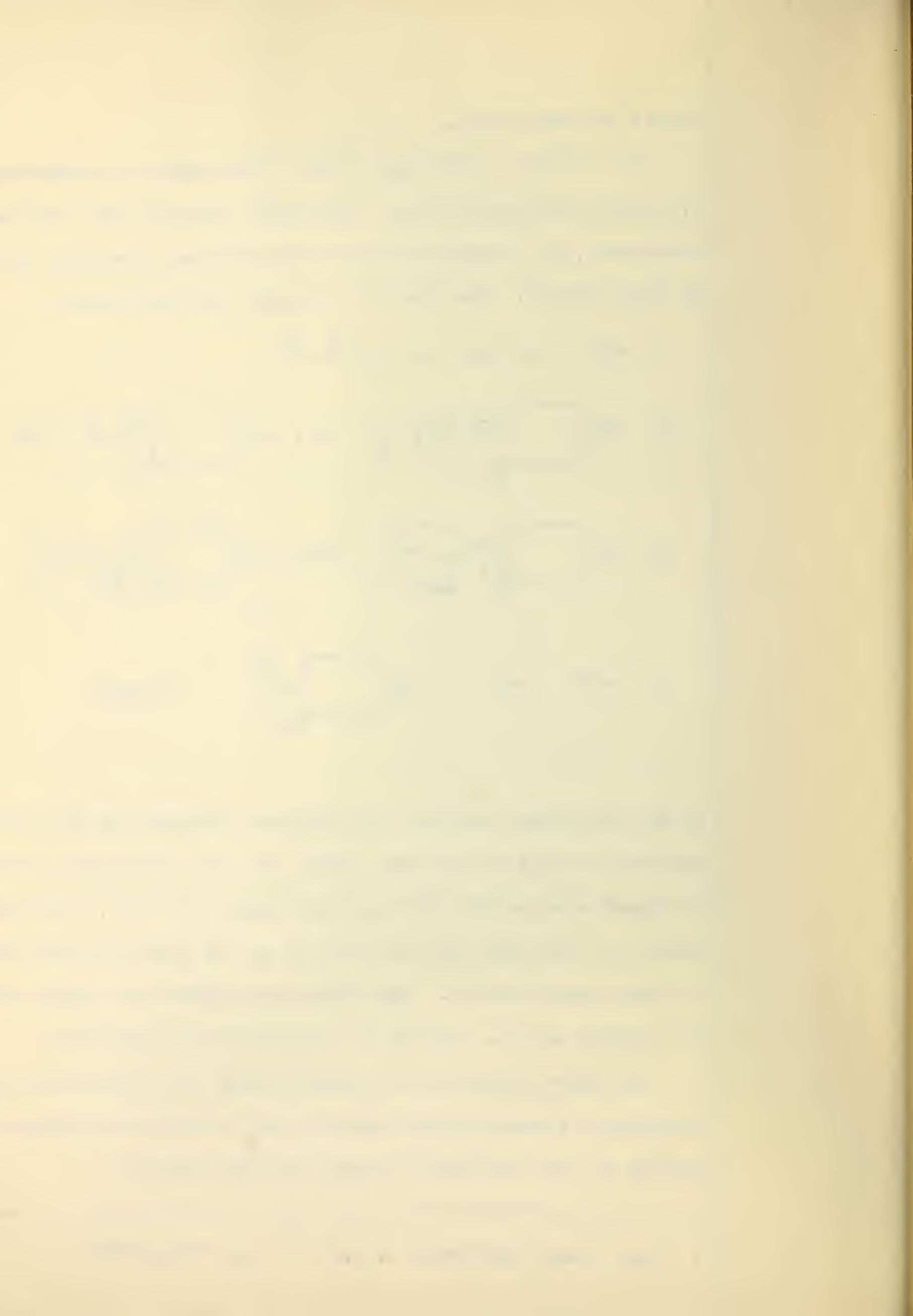
As a result of the above work it was hoped to synthesize 2,4-dihydroxyphenylalanine. Resorcylic aldehyde was prepared from resorcinol, by a modification of the Gatterman reaction, proposed by Roger Adams⁹. The reaction proceeds as shown below:-

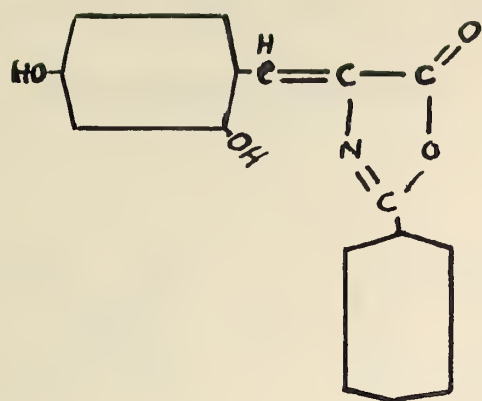


In the Gatterman reaction, dry hydrogen chloride and dry hydrogen cyanide are used to form the imide. In the modification proposed by Adams⁹ a suspension of dry zinc cyanide in ether, into which is passed dry hydrogen chloride, serves as the agent to form the imide or imide hydrochloride. The dihydroxyaldehydes are water soluble, to a slight extent, and may be recrystallized from water.

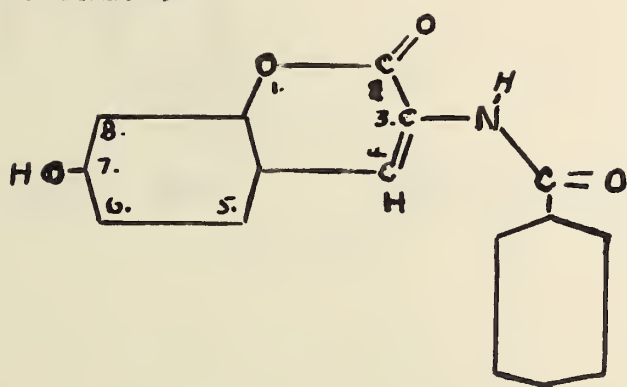
The above aldehyde was passed through the Erlenmeyer Jr. reaction involving a reaction with hippuric acid to form an azlactone corresponding to the structural formula as shown below:-

9. Roger Adams and Levine J. A. C. S. 45, 2373, (1923)

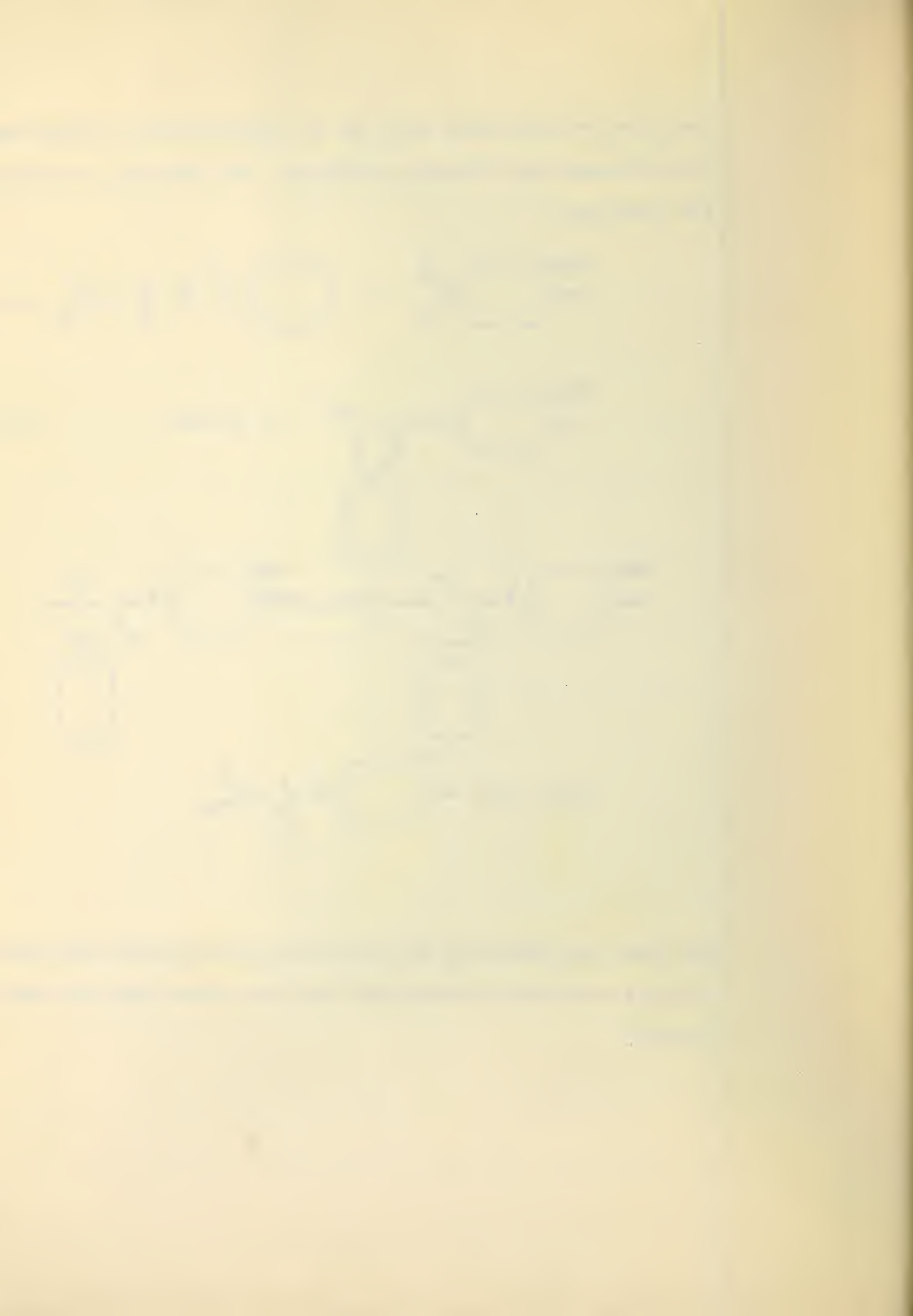




Attempts to form the free acid from the above azlactone by alkaline hydrolysis and neutralization led to the formation of a coumarin, 3-benzoylamino-7-hydroxycoumarin. It is likely that the free acid was formed but rapidly changed to the coumarin with the elimination of water. Hydrolysis, of the above azlactone with dilute and concentrated hydriodic acid, yielded the coumarin only. Consequently, it was found impossible by this method to form 2,4-dihydroxyphenylalanine:-



Harrington and McArtney prepared 3,4-dihydroxyphenylalanine from vanillin by, first, an Erlenmeyer Jr. reaction, secondly, the formation of the ethyl ester of β -(3-methoxy-4-hydroxy)- α -benzoyl-aminopropionic acid, and finally the reduction of the above ester by refluxing with concentrated hydriodic acid and red phosphorous. The synthesis, of the above amino acid, required much time. At least, one week is necessary for the precipitation of the ester. By preparing the free acid from the azlactone, and treating it with



EXPERIMENTAL PART ONE

Iodine Monochloride. - Chlorine gas, generated from potassium permanganate, was passed over one g. mole. of iodine until the uptake of chlorine was equal to one g. atom. This gave a dark brown liquid, sufficiently pure for the iodination of benzene derivatives.

2,6-Diiodo-p-Nitroaniline. - The procedure as developed below is to appear in the forthcoming issue of "Organic Synthesis."

Fifty g. (0.36 g. mole.) of technical p-nitroaniline was dissolved in 100 cc. of boiling glacial acetic acid in a 1.5 l. beaker (Note 1). To this hot solution (the outside source of heat was removed) was added in a slow steady stream with vigorous stirring, (Note 2) a solution of 150 g. (0.92 g. mole.) of iodine monochloride (Note 3) in 25 cc. of glacial acetic acid. Considerable heat was generated and hydrogen chloride, acetic acid, and iodine fumes were given off. The mixture was allowed to stand on a boiling water bath for two hours. It was then cooled and to the reaction mixture which was quite solid, was added 50 cc. of glacial acetic acid. The hard lumps were crushed thoroughly with a glass stopper and the whole mass of crystals filtered off by suction, using 25 cc. of glacial acetic acid to transfer the last of the crystals to the funnel. The diiodo-p-nitroaniline was then transferred back into the original beaker and to it was added 100 cc. of cold glacial acetic acid. It was thoroughly stirred and once more filtered off by suction. The beaker was then rinsed out with 50 cc. of cold glacial acetic acid and the crystals were again sucked as dry as

possible. The yield, of air-dried material, was 112-125 g. (79-89% of the theoretical). The diiodo-p-nitroaniline, thus prepared, formed yellow crystals, m. p. 243° (unc.).

Notes. 1. A beaker of this size was used to prevent the reaction mixture from boiling over.

2. It was advisable to wear rubber gloves during this operation.

3. Iodine monochloride was prepared as shown above.

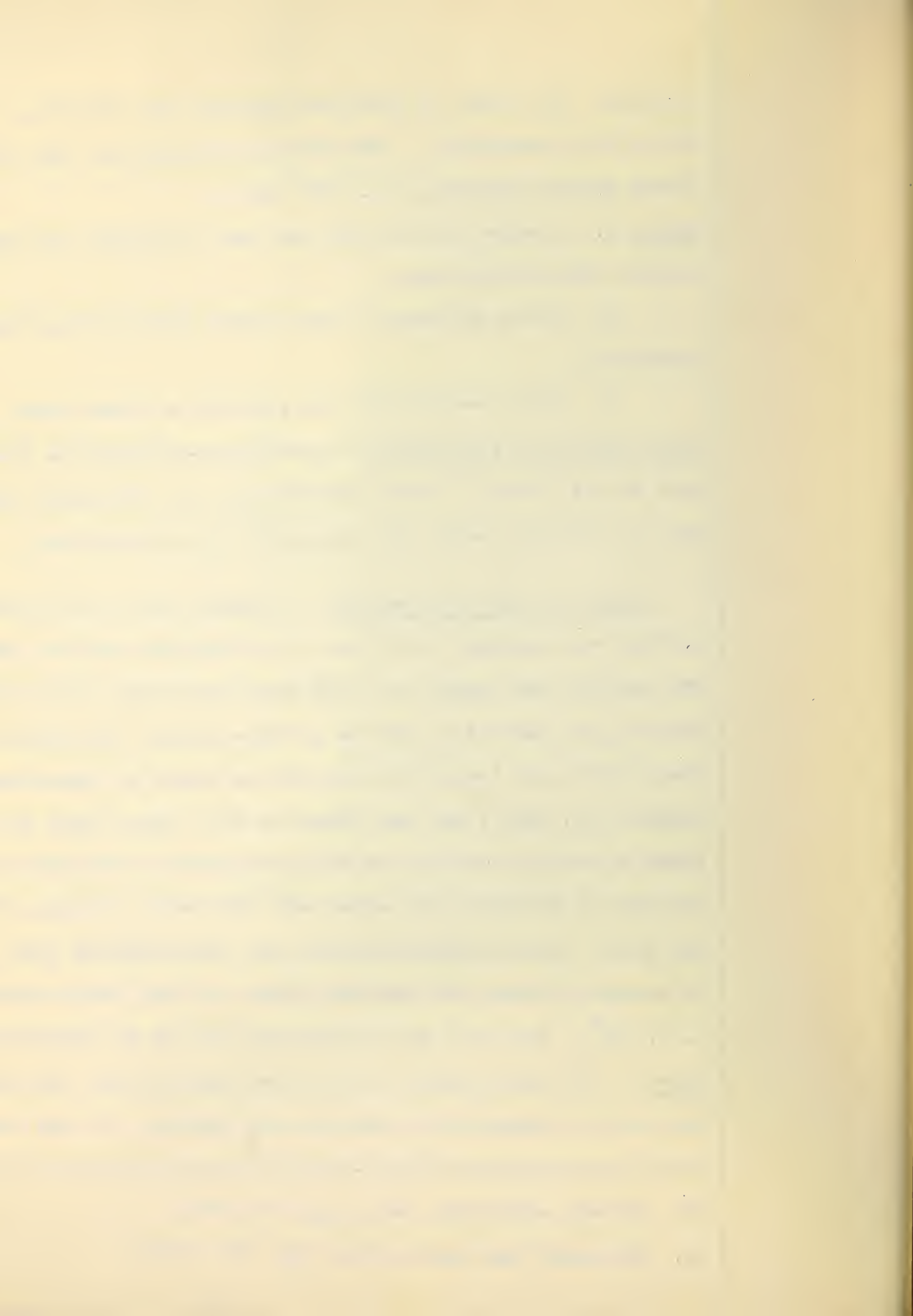
Other Methods of Preparation. -2,6-diiodo-p-nitroaniline has been made by the action of iodine monochloride on a chloroform solution¹⁰ and on a glacial acetic acid solution¹¹ of p-nitroaniline.

3,4,5-Triiodo Nitrobenzene². - Seventy five g. of 2,6-nitroaniline was dissolved in 150 cc. of concentrated sulfuric acid. The solution was cooled to 5° and diazotized using sodium nitrite. Stirring was carried on for two or three hours. The mixture was then poured onto ice and treated with an excess of potassium iodide (5 g. mole.) and then heated to 65° . Free iodine was removed by sodium bisulfite and the precipitate of triiodonitrobenzene was filtered off, washed well with water, alcohol, ether and dried. The triiodonitrobenzene was recrystallized from acetone or benzene yielding well defined yellow to light brown crystals, m. p. 165° . The yield was approximately 75% of the theoretical.

Notes. - The diazotization of the above amine did not take place very well in concentrated sulfuric acid solution. It was found

10. Michael and Norton, Ber., 11, 113 (1878).

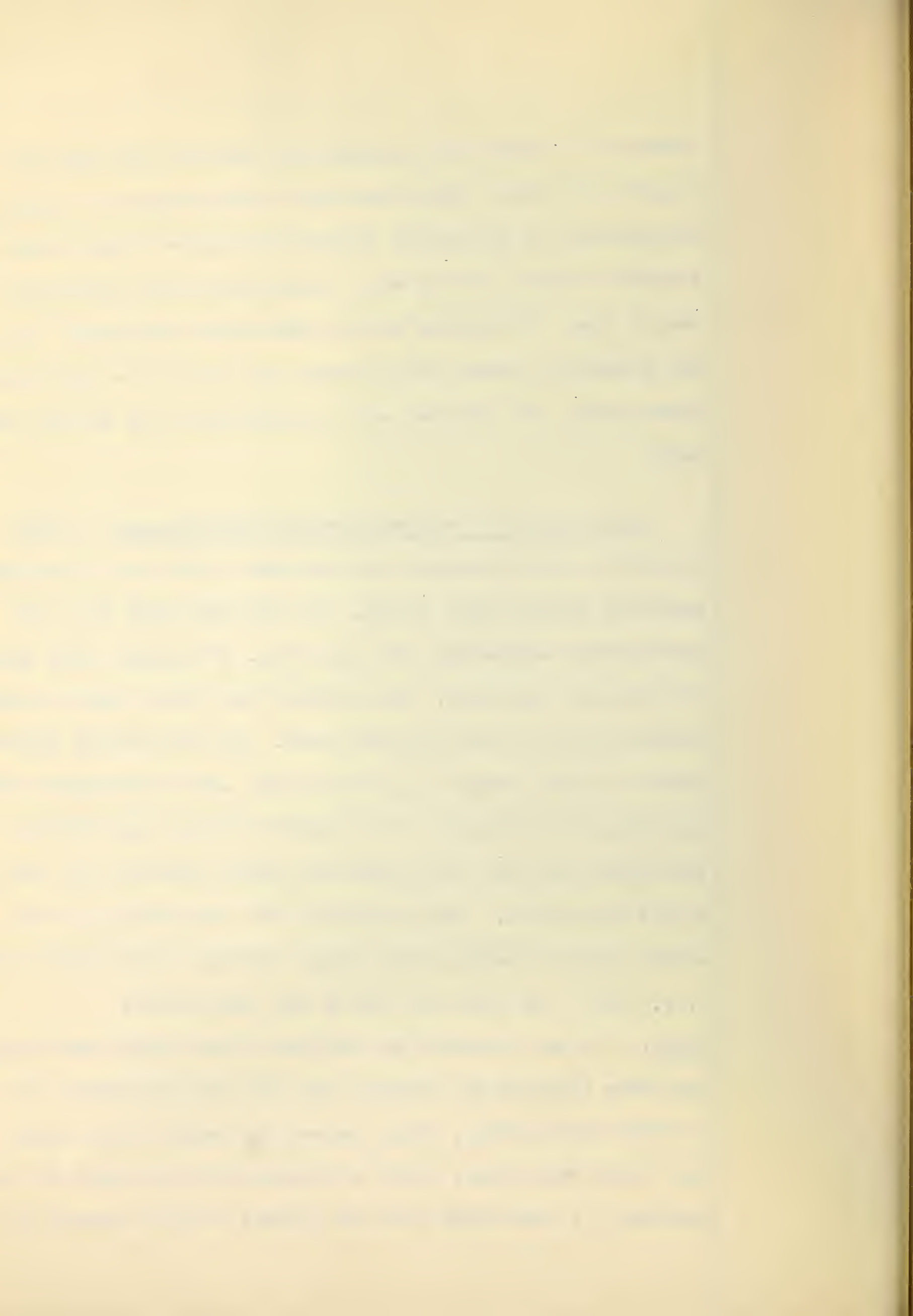
11. Willgerodt and Arnold, Ber., 34, 3344 (1901).



advisable to dilute the concentrated sulfuric acid with an equal quantity of water. When there was a large amount of diiodo-p-nitroaniline in the impure triiodonitrobenzene it was found advisable to carry out the above diazotization and iodination a second time. The method used by Harrington and Barger² to purify the product by vacuum distillation was found to be unsatisfactory. Consequently the compound was recrystallized from acetone or benzene.

3,5-Diiodo-4-(4'-Methoxyphenoxy)-Nitrobenzene. - Fifty g. of 3,4,5-triiodonitrobenzene was dissolved in 250 cc. of boiling anhydrous methyl ethyl ketone. To this was added 25 g. of hydroquinone monomethyl ether and 30 g. of freshly dried and powdered potassium carbonate. This mixture was boiled under a reflux condensor for at least sixteen hours. To the reaction mixture was added a slight excess of glacial acetic acid to decompose the remaining potassium carbonate. The reaction mixture was filtered hot, then cooled and the nitro-compound, which separated out, was filtered off by suction. The precipitate was recrystallized from glacial acetic acid and methyl ethyl ketone yielding light yellow crystals, m. p. 144^o. The yield was 65% of the theoretical.

Notes. - In the procedure as outlined by Harrington and Barger², the above compound was removed from the reaction mixture by a method of steam distillation, which removed the methyl ethyl ketone leaving a dark tarry mass, which on recrystallization gave the nitro-compound. It was found that the product could be secured by the

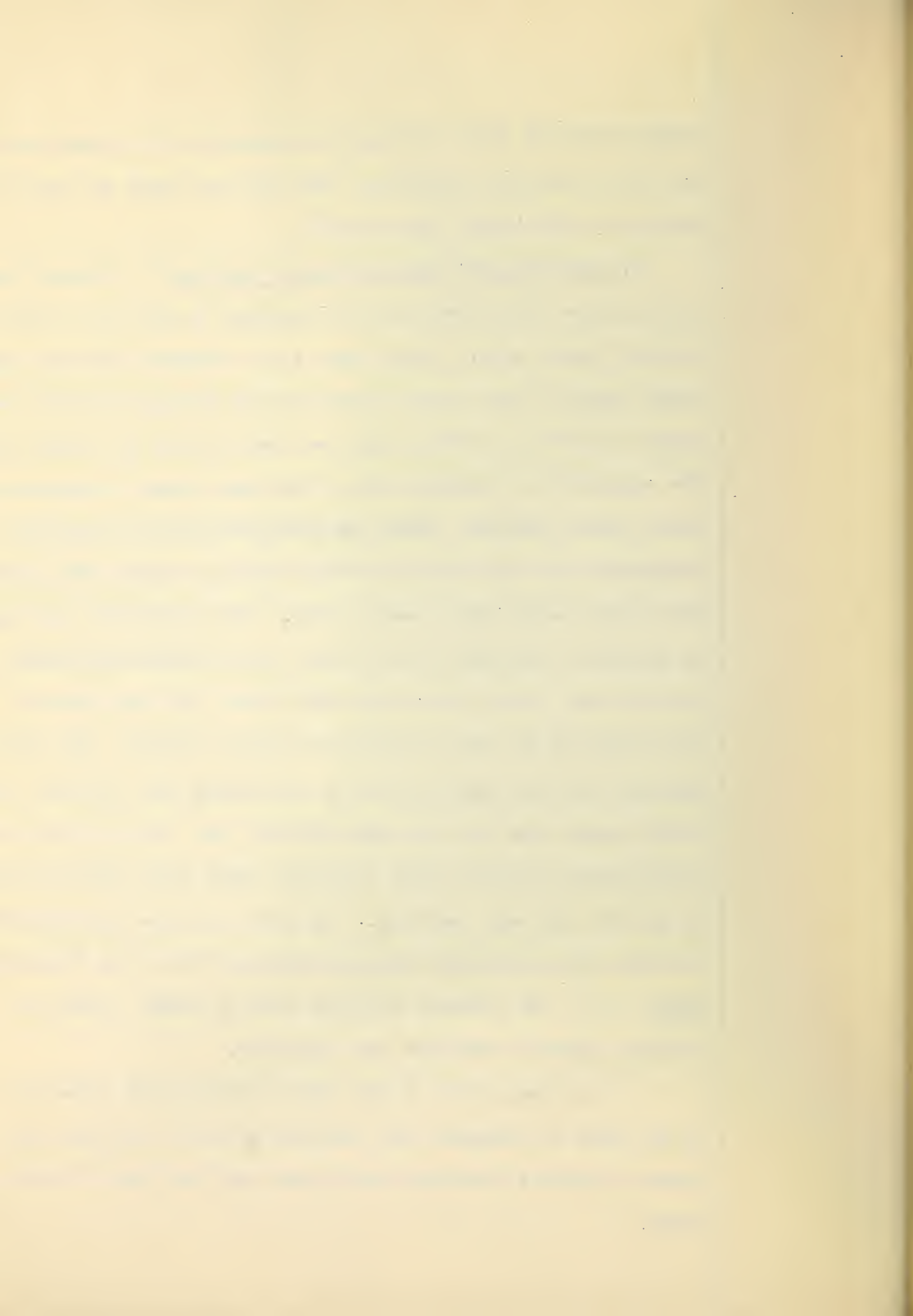


method outlined above without the necessity of a steam distillation and free from tarry products. The yield was much the same as that secured by Harrington and Barger².

3,5-Diiodo-4-(4'-Methoxyphenoxy)-Aniline.² - Twenty five g. of the above nitro-compound was dissolved in 125 cc. of boiling glacial acetic acid. Forty three g. of stannous chloride was added (Note 1) and a rapid stream of dry hydrogen chloride was passed into the solution, which was kept heated on a water bath. The crystalline stannichloride of the base began to separate in about thirty minutes. When the precipitation was completed, the stannichloride was filtered off by suction, washed with cold glacial acetic acid and allowed to dry. The precipitate was decomposed by grinding thoroughly with 250 cc. of 40% sodium hydroxide. This solution was cooled, extracted with ether, and the ethereal solution dried by the use of anhydrous sodium sulfate. The amine hydrochloride was precipitated by saturating the ethereal solution of the amine with dry hydrogen chloride gas. The hydrochloride precipitated as white flaky crystals, which were sufficiently pure to use for the next reaction. The yield of amine hydrochloride from the nitro-compound was approximately 60% of the theoretical.

Notes. - 1. The stannous chloride must be added slowly or the reaction mixture overflows the container.

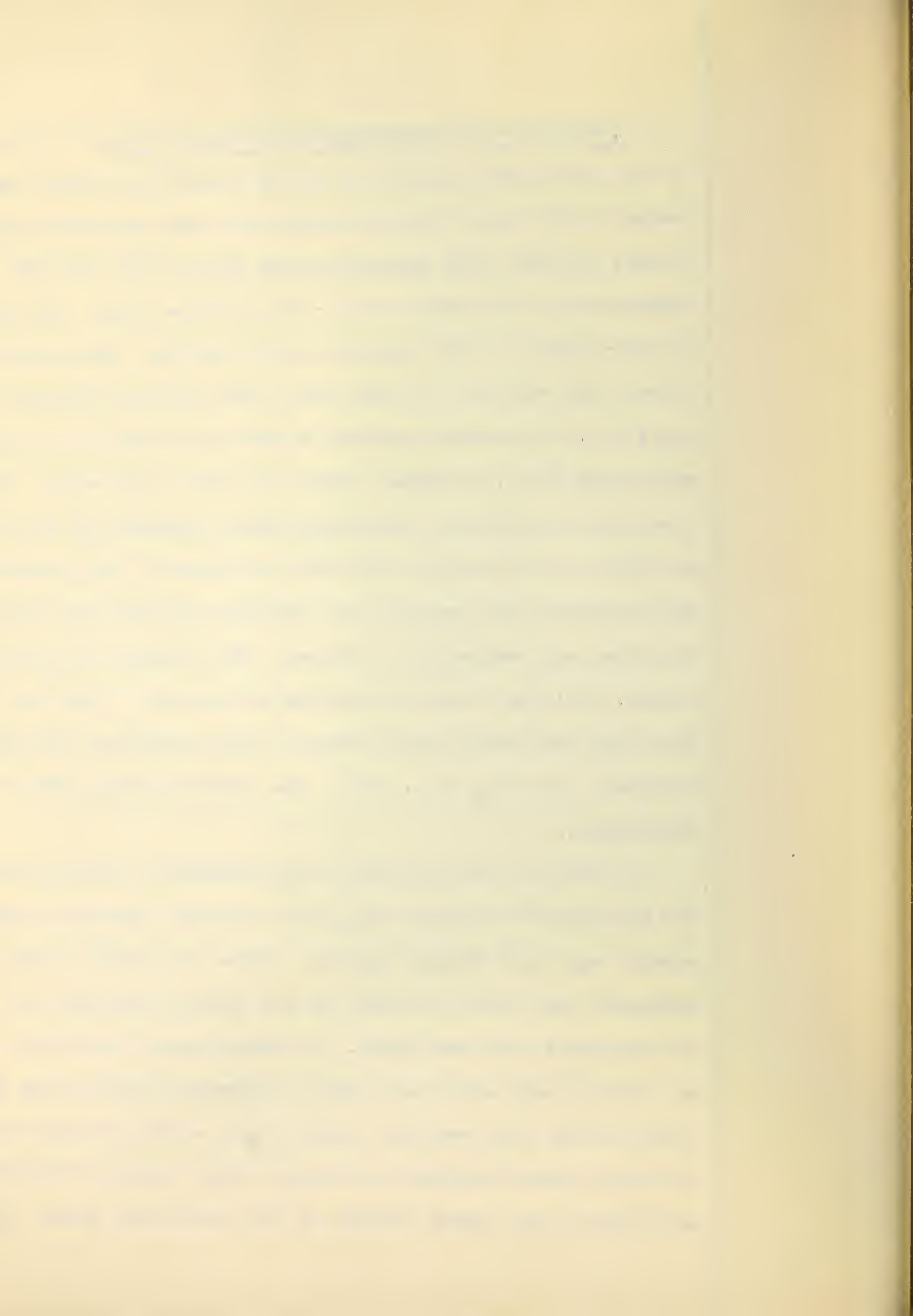
2. The purity of the amine hydrochloride seems to depend on the time to decompose the stannichloride of the base, the time taken to extract the amine with ether and the time of drying the amine.



3,5-Diiodo-4-(4'-Methoxyphenoxy)-Benzonitrile.² - Thirty g.

of the above hydrochloride was ground finely in a mortar and suspended in 300 cc. of glacial acetic acid and diazotized using isoamyl nitrite. The temperature was kept at 15° - 20° and the diazotization was carried on for two to three hours. An orange to red solution of the diazonium salt resulted. This solution was poured with vigorous stirring into a hot solution prepared by adding 170 g. of potassium cyanide in 300 cc. of water to a solution containing 150 g. of copper sulfate in 600 cc. of water. The resulting precipitate, containing cuprous cyanide and the nitrile, was filtered off, washed with water and dried. The precipitate was extracted with benzene, the solution was dried over calcium chloride, and evaporated to dryness. The residue was distilled in vacuo, yielding a dark crystalline precipitate. This was recrystallized from methyl ethyl ketone, using bone-black and yielded colorless crystals, m. p. 166°. The yield was about 35% of the theoretical.

A number of modifications of the Sandmeyer reaction were tried. The Korczinski⁵ reaction using nickel cyanide instead of cuprous cyanide was tried without success. Other reactions⁶, using sodium carbonate and sodium hydroxide in the cyanide solutions to take care of the excess acid were tried. In these cases, the nitrile formed as a fairly dark solid mass which upon vacuum distillation yielded a dark brown, foul smelling liquid, which would not give crystals of nitrile upon treatment with methyl ethyl ketone. Diazotizations were tried using sodium nitrite as the diazotizing agent. Formic



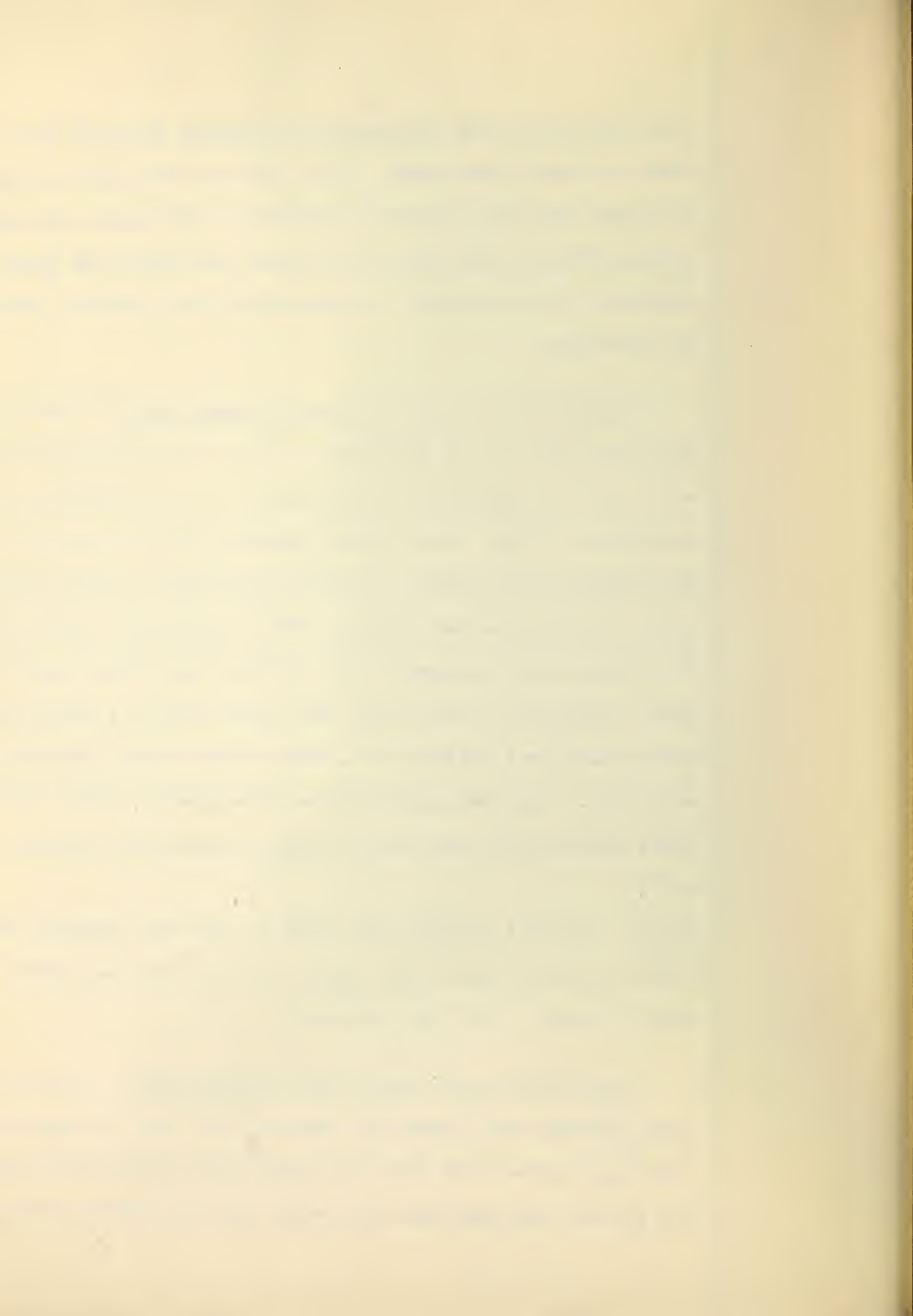
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acid and acetic acid saturated with hydrogen chloride were also tried as diazotizing media. In no case was the yield as good as the yield from the procedure developed by Harrington and Barger². Consequently, it was decided to follow Harrington and Barger's procedure in the attempt to prepare the other nitriles, the isomers of the above.

3,5-Diiodo-4-(4'Methoxyphenoxy)-Benzaldehyde.² -Five g. of the above nitrile was dissolved in 35 cc. of chloroform and added with vigorous shaking to a solution of 12 g. of anhydrous stannous chloride in 60 cc. of dry ether saturated with hydrogen chloride. The solution was allowed to stand for at least sixteen hours and the yellow precipitate was filtered off by suction and washed with ether. The precipitate was warmed with a little very dilute hydrochloric acid. Hydrolysis immediately took place and the aldehyde which precipitated was filtered off, washed with dilute hydrochloric acid and dried. Upon recrystallization from glacial acetic acid there was a practically quantitative yield of colorless crystals, m. p. 121°.

Notes. - Various attempts were made to form the aldehyde from chloroform solutions of the impure nitrile from the former reaction. These, however, were not successful.

Azlactone from the above and Hippuric Acid². - Five g. of the above aldehyde was ground in a mortar with 5 g. of hippuric acid, and then treated with 15 cc. of freshly distilled acetic anhydride. The mixture was kept warm on a water bath for fifteen minutes. The



yellow precipitate was ground thoroughly with 150 cc. of warm water to decompose the acetic anhydride, filtered off by suction, washed well with water and dried. The yield was quantitative forming yellow crystals melting at 211° . This step did not present any difficulties.

α -Benzoylamino-3,5-Diiodo-4-(4'-Methoxyphenoxy)-Cinnamic Acid

Ethylester.² - The azlactone as prepared above was dissolved in 50 - 75 parts of absolute ethyl alcohol, containing 10% of sulfuric acid by weight. The resulting clear colorless solution was filtered and poured into distilled water. The ester which separated out was filtered off, washed well with water and dried. The yield was practically quantitative and on recrystallization from methyl ethyl ketone gave colorless needles, m. p. 202.5° . This step was very smooth.

3,5-Diiodo-4-(4' Methoxythiophenoxy)-Nitrobenzene.¹ - Fifty g. (0.1 g. mole.) of 3,4,5-triiodonitrobenzene^{2,12} and 14 g. (0.1 g. mole.) of p-methoxythiophenol¹³ was added to 250 cc. of boiling methyl ethyl ketone. To this mixture was added 30 g. of finely powdered dry potassium carbonate. After heating under a reflux condensor in a current of hydrogen gas for five hours the hot reaction mixture was filtered. On cooling the filtrate, bright yellow crystals of the pure nitro-compound were formed. A further crop of

12. Kalb, Schweizer, Zellner and Berthold, Ber., 59, 1869 (1926).

13. From p-anisidine, Leuckart, J. Prakt. Chem., 41, 179 (1890).

crystals was obtained by evaporating off the mother liquor. On recrystallization from acetone or methyl ethyl ketone there was secured a 60 - 65% yield of the theoretical, m. p. 138-139° (corr.).

3,5-Diiodo-4-(4'-Methoxythiophenoxy)-Aniline Hydrochloride¹⁴. -

Twenty five g. of the above nitro-compound was dissolved in 125 cc. of hot glacial acetic acid. Forty three g. of stannous chloride was added and a rapid stream of dry hydrogen chloride was passed into the solution which was kept hot on a water-bath. The white stannichloride of the base began to separate in twenty five to thirty minutes. When the precipitation was complete the stannichloride was filtered off and dried in an air oven at 50°. The precipitate was then rapidly decomposed using 250 cc. of 40% sodium hydroxide. This mixture was rapidly cooled and extracted with ether. The ethereal solution was slightly colored. It was dried over anhydrous sodium sulfate and the amine-hydrochloride was precipitated by passing a stream of dry hydrogen chloride into the solution. There was secured a practically quantitative yield of white flakes which decomposed at 200°.

3,5-Diiodo-4-(4'-Methoxythiophenoxy)-Benzonitrile. - A number of attempts were made to form this compound. The procedure outlined by Harrington and Barger² for the corresponding oxygen nitrile was followed several times without success. In every case the preparation seemed to fail during the vacuum distillation. Yields of from 1 - 2 g. of a compound, which gave a halogen analysis 2 - 3% low, were secured.

14. Drake, Thesis work, (1929).

Modifications of the Sandmeyer reaction proposed by Korczinski⁵ and McRae⁶ were followed but did not give the desired nitrile. Since those attempts were unsuccessful it was decided to abandon the attempt to prepare this nitrile.

3,5-Diiodo-4-(3'-Methoxyphenoxy)-Nitrobenzene.¹⁴ - This compound was prepared from resorcinol monomethyl ether and 3,4,5-triiodo-nitrobenzene^{2 12} by the method given by Harrington and Barger² for the corresponding 4'-methoxy-nitro-compound. The yield was 45-50% of the theoretical of light brown crystals, m. p. 139-140° (corr.).

3,5-Diiodo-4-(3'Methoxyphenoxy)-Aniline Hydrochloride.¹⁴ - This compound was prepared from the above nitro-compound by a reduction using stannous chloride and anhydrous hydrochloric acid given by Harrington and Barger² for the corresponding 4'-methoxy-amino-compound. The yield of hydrochloride from the nitro-compound was 60% of the theoretical of gray flaky crystals, dec. 132-134°.

3,5-Diiodo-4-(3'-Methoxyphenoxy)-Benzonitrile. - Attempts to prepare this nitrile were made as in the case of the thio-nitrile above. However, these were not successful.

EXPERIMENTAL PART TWO

p-Nitrochlorbenzene. - This compound was prepared from p-nitro-aniline by a Sandmeyer reaction¹⁵. The impure p-nitrochlorbenzene was purified by steam distillation giving a yield of colorless to light yellow crystals, m. p. 83°.

p-Hydroxybenzaldehyde. - This compound was prepared from the practical, by a number of recrystallizations from water using bone-black to remove oxidation products. The final product was of a pink color, m. p. 114.75°.

Potassium Salt of p-Hydroxybenzaldehyde⁷. - A solution of 25 g. of potassium hydroxide in 25 cc. of hot water was added with stirring to 97 g. of p-hydroxybenzaldehyde in 200 cc. of absolute alcohol. The mixture was cooled in ice giving a dark red precipitate 90% of the theoretical, which was suitable for the following reaction.

4-(4'-Nitrophenoxy)-Benzaldehyde⁷. - To 200 g. (1.27 g. mole.) of p-nitrochlorbenzene kept at 160-170° in an oil bath was added in small portions with stirring during one hour 93 g. (0.58 g. mole.) of the dry potassium salt as prepared above. The mixture was maintained at 200° for six hours, cooled and steam distilled to remove the excess p-nitrochlorbenzene. One recrystallization from dilute acetic acid produced 120 g. (75% of the theoretical) of a light brown product. A second recrystallization from alcohol using bone-black produced yellow needle-like crystals, m. p. 104-105°.

Azlactone from the above Aldehyde.- Twelve and one tenth g. of the above aldehyde was ground thoroughly in a mortar with 8.75 g. of hippuric acid and 7.5 g. of sodium acetate. The above mixture was treated with 30 cc. of acetic anhydride and allowed to stand on a water-bath for one hour. The azlactone formed and precipitated out. The reaction mixture was treated with 300 cc. of warm water and the yellow precipitate was filtered off, washed with water and dried. The yield of practically pure azlactone was 98.6% of the theoretical. A further recrystallization from glacial acetic acid gave yellow crystals, m. p. 176° (corr.). The yield after recrystallization was 75-80% of the theoretical.

Anal. Calcd. for $C_{22}H_{14}O_5N_2$: C, 68.3, H, 3.6. Found: C, 68.49, H, 3.83.

α -Benzoylamino-4-(4'-Nitrophenoxy)-Cinnamic Acid Ethylester. -

This ester was prepared from the above azlactone by refluxing 15 g. of the azlactone with 500 cc. of absolute alcohol containing 10% of sulfuric acid by weight. After two hours the green solution formed above was filtered and added to a large excess of water. The ester separated as greenish gum, which solidified overnight and could be filtered off by suction. The solid upon recrystallization from alcohol using boneblack gave colorless needles, m. p. 165.7° (corr.). The yield was approximately 50% of the theoretical.

Anal. Calcd. for $C_{24}H_{20}N_2O_6$: C, 66.66, H, 4.62. Found: C, 66.50, H, 4.63.

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α -Benzoylamino-4-(4'-Nitrophenoxy)-Cinnamic Acid. - Five g. of the azlactone was heated on a water-bath for two hours with an excess of dilute sodium hydroxide and a few cc. of alcohol. The resulting clear yellow solution was cooled by the addition of ice and made acid with dilute sulfuric acid. The free acid immediately precipitated and was filtered off. Upon recrystallization from dilute acetic acid there was a 75% of the theoretical yield of minute colorless crystals, m. p. 209.3° (corr.) with sintering at 204° .

Anal. Calcd. for $C_{22}H_{16}O_5N_2$: C, 65.3, H, 3.93. Found: C, 65.6, H, 4.03.

2,4-Dihydroxybenzaldehyde.⁹ - The catalyst used in the Gatterman reaction was zinc cyanide.

Zinc Cyanide. - One g. mole. of potassium cyanide was dissolved in the minimum quantity of water. To this was added 7 - 8% of 1 g. mole. of magnesium chloride. The white precipitate of magnesium carbonate and magnesium hydroxide was immediately filtered off and to the filtrate was added 1 g. mole. of zinc chloride dissolved in the minimum quantity of 50% alcohol. The white precipitate of zinc cyanide was immediately filtered off, washed with alcohol and ether and dried. This procedure yielded absolutely pure zinc cyanide suitable for the Gatterman reaction below.

Notes. - Potassium cyanide seemed to be a better reagent than sodium cyanide since the former is purer than the latter.

2,4-Dihydroxybenzaldehyde. - To twenty g. of 1, 3-dihydroxybenzene was added 17 - 18 g. of zinc cyanide and the mixture was suspended in 150 - 200 cc. of anhydrous ether. Dry hydrogen chloride gas was passed in for two hours. The mixture was vigorously stirred during the addition of hydrogen chloride. The imide-hydrochloride separated out as a thick oil which finally turned solid. The ethereal solution, containing the colored impurities, was decanted off. To the precipitate was added 150 cc. of water. The mixture was heated to boiling, filtered and cooled. The aldehyde precipitated in brown platelets, which upon recrystallization from water gave a 78% of the theoretical yield of nearly colorless crystals, m. p. 136°.

Notes. - In the procedure as given by Adams and Levine⁹ it was advised to use twice the above quantity of zinc cyanide. One run was made in this manner with unsatisfactory results. Thus it was decided to use the theoretical quantity of zinc cyanide. The above reaction must be carried out in a special apparatus to prevent the escape of hydrogen cyanide gas.

Azlactonemonoacetate from the above Aldehyde. - Thirteen and eight tenths g. of 2,4-dihydroxybenzaldehyde was ground in a mortar with 17.9 g. of hippuric acid and 15 g. of sodium acetate. To this was added 30 cc. of acetic anhydride. The mixture was heated on a water-bath for two hours. To the resulting mixture was added 300 cc. of warm water. The yellow azlactone was filtered

off, washed well with water and dried. Upon recrystallization from dilute acetic acid there was an 80% of the theoretical yield of yellow flaky azlactonemonoacetate, m. p. 190° (corr.). For analytical purposes and to separate the monoacetate and diacetate it was necessary to recrystallize four times from acetic acid.

Anal. Calcd. for $C_{18}H_{13}O_5N$: C, 66.87, H, 4.02. Found: C, 66.93, H, 4.10.

3-Benzoylamino-7-Hydroxycoumarin. - Every case in which the azlactone ring was broken by alkaline hydrolysis or acid hydrolysis yielded this coumarin. The coumarin was insoluble in water and but slightly soluble in warm alcohol. It did not melt in the temperature range of a glycerol bath.

Anal. Calcd. for $C_{16}H_{11}O_4N$: C, 68.3, H, 3.91. Found: C, 68.4, H, 4.09.

Azlactone from Vanillin.⁴ - Fifteen and two tenths g. of vanillin was ground thoroughly in a mortar with 17.9 g. of hippuric acid and 15 g. of sodium acetate. The mixture was treated with 30 cc. of acetic anhydride and heated on a water-bath for fifteen minutes. The reaction mixture was ground thoroughly with 300 cc. of warm water and the yellow azlactone was filtered off, well washed with water and dried. Upon recrystallization from glacial acetic acid there was a 75% of the theoretical yield of yellow needles, m. p. 189° .

3-Methoxy-4-Hydroxy- α -Benzoylamino-Cinnamic Acid. - Ten g. of

the above azlactone was dissolved in dilute sodium hydroxide and heated on a water-bath for one hour. The clear solution was filtered and cooled by the addition of ice and neutralized by the addition of a slight excess of dilute sulfuric acid. On recrystallization of the precipitate free acid from dilute alcohol, using boneblack there was secured a practically quantitative yield of colorless crystals, m. p. 213.4° , sintering at 209° .

Anal. Calcd. for $C_{17}H_{15}O_5N$: C, 65.14, H, 4.79. Found: C, 65.55, H, 4.92.

3,4-Dihydroxyphenylalanine. - Ten g. of the above free acid was refluxed for one and one half hours with 25 cc. of hydriotic acid concentrated and 25 cc. of glacial acetic acid and 5 g. of red phosphorous in a current of methane. The solution was filtered hot and evaporated to dryness in vacuo, again in a current of methane. The benzoic acid was removed by extraction with ether and the aqueous solution of the residue was neutralized with ammonia and again evaporated to dryness in vacuo. The residue was dissolved in a little water and a large amount of alcohol was added to precipitate the pigment which was filtered off. The solution was again evaporated to dryness in vacuo. The residue was dissolved in a little warm water containing sulfur dioxide. The solution was boiled with boneblack filtered and allowed to cool in a vacuum dessicator. There was a 50% yield of the theoretical of slightly colored platelets, m. p. $272.5 - 273.5^{\circ}$ with decomposition.

SUMMARY

1. Attempts were made unsuccessfully to prepare 3,5-diiodo-4-(3'-methoxyphenoxy)-benzonitrile and 3,5-diiodo-4-(4'-methoxythiophenoxy)-benzonitrile.

2. A number of new compounds, derivatives of 4-(4'-nitrophenoxy)-benzene, were prepared and some properties were recorded.

3. 2,4-Dihydroxyphenylalanine could not be prepared due to the formation of a coumarin which was isolated.

4. A new procedure has been developed for the preparation of 3,4-dihydroxyphenylalanine.

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